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Code: 5000-72136

JAPANESE PATENT OFFICE
PATENT JOURNAL
KOKAI PATENT APPLICATION NO. HEI 10[1998]-287532

Int. Cl.[6]:	A 61 K 7/06 31/557 //A 61 K 31/557
Application No.:	Hei 9[1997]-100091
Application Date:	April 17, 1997
Publication Date:	October 27, 1998
No. of Claims:	7 (Total of 6 pages; OL)
Examination Request:	Not requested

AGENT FOR HAIR GENERATION AND GROWTH

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Abstract

Objective

To offer an agent for hair generation and growth that has excellent effects.

Means to solve

An agent for hair generation and growth that has a 15-ketoprostaglandin compound as its effective component.

Claims

1. An agent for hair generation and growth that has a 15-ketoprostaglandin compound as its effective component.

2. The agent for hair generation and growth according to Claim 1, wherein the 15-ketoprostaglandin compound is a 13,14-dihydro-15-ketoprostaglandin compound.

3. The agent for hair generation and growth according to Claim 1, wherein the 15-ketoprostaglandin compound is a 15-keto-16-mono- or dihaloprostaglandin compound.

4. The agent for hair generation and growth according to Claim 1, wherein the 15-ketoprostaglandin compound is a 13,14-dihydro-15-keto-16-mono- or dihaloprostaglandin compound.

5. The agent for hair generation and growth according to Claim 1, wherein the 15-ketoprostaglandin compound is a 15-keto-16-mono or difluoroprostaglandin compound.

6. The agent for hair generation and growth according to Claim 1, wherein the 15-ketoprostaglandin compound is a 13,14-dihydro-15-keto-16-mono- or difluoroprostaglandin compound.

7. The agent for hair generation and growth according to Claim 1, wherein the 15-ketoprostaglandin compound is a 15-ketoprostaglandin E compound.

Detailed explanation of the invention

[0001]

Technical field of the invention

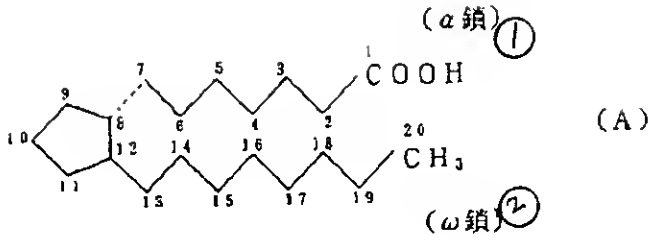
This invention concems the novel use of 15-ketoprostaglandin in hair generation and growth.

[0002]

Prior art

Prostaglandins (prostaglandins are referred to below as "PGs") are contained in the tissues and organs of humans and other mammals, and are a group of organic carboxylic acids that exhibit a broad range of physiological activities. PGs that are present in the natural world have the common structural feature of a prostanoic acid skeleton as expressed by formula (A).

[0003]
[Structure 1]



(A)

Key: 1 (α chain)
2 (ω chain)

[0004]

On the other hand, a number of synthetic analogs have derivative skeletons. Natural PGs are classified into PGAs, PGBs, PGCs, PGDs, PGEs, PGFs, PGGs, PGHs, PGIs and PGJs in accordance with thc structural features of the five-membered ring. In addition, the compounds are also classificd into:
subclassification 1: 13,14-unsaturated-15-OH compounds;
subclassification 2: 5,6- and 13,14-diunsaturated-15-OH compounds; and
subclassification 3: 5,6-, 13,14- and 17,18-triunsaturated-15-OH compounds.

[0005]

PGFs arc also classificd into α types (hydroxyl group in the α configuration), and β types (hydroxyl group in thc beta configuration) depending on the location of the hydroxyl group of position 9. It is known that PGE 1 and PGI 2 have the action of stimulating hair generation (Japanese Kokai Patent Application No. Sho 61[1986]-218510), and that beraprost [transliteration] and other PGI 2 derivatives have hair generation and growth effects (Japanese Kokai Patent Application No. Hei 5[1993]-331025). Moreover, a number of 15-keto PGs (specifically, those having an oxo group instead of a hydroxyl group at position 15) and 13,14-dihydro-15-keto PGs are known to have physical properties whereby they are naturally produced by means of enzymes in the metabolism of natural PG. Furthermore, 15-keto PG compounds have been described in Japanese Kokai Patent Application Nos.
Hei 1[1989]-104040, Sho 64[1989]-52753, Hei 1[1989]-151552 and Hei 8[1996]-48665.

However, 15-keto PG compounds are currently not known to have hair generation and hair growth effects.

[0006]

Problems to be solved by the invention

This invention has the objective of offering an agent for hair generation and growth which has excellent effects.

[0007]

Means to solve the problems

The inventors of the present invention, as a result of investigations concerning the biological activity of 15-keto PG compounds, arrived at the present invention upon discovering that these compounds can be used in treatments aimed at stimulating hair generation and growth. Specifically, this invention offers an agent for hair generation and growth having a 15-ketoprostaglandin compound as its effective component. Thus, the agent for hair generation and growth of the present invention is effective in the treatment of baldness and hair growth deficiencies.

[0008]

In the present invention, the term "treatment" includes any type of disease management, including prevention, therapeutic treatment, abatement, dramatic halting, and dramatic reduction. The term "15-ketoprostaglandin compound" is abbreviated below as "15-keto PG compound", but also includes any prostaglandin derivative having an oxo group instead of a hydroxyl group at position 15 of the prostanoic acid skeleton, regardless of whether a double bond is present between positions 13 and 14.

[0009]

The number of the prostanoic acid represented in formula (A) is used for naming the 15-keto PG compounds of the present invention. Formula (A) above is a compound having a basic skeleton with twenty carbon atoms, but in the present invention the carbon number is not restricted. Specifically, the numbers of the carbon atoms that constitute the basic skeleton start with the carboxylic acid as 1, with numbers 2-7 in sequence towards the five-membered ring assigned to the α chain carbons, 8-12 assigned to the carbon atoms of the five-membered ring, and 13-20 assigned to the ω chain. However, when the number of carbons decreases due to the α chain, the sequential numbers are eliminated from position two, and when there is an increase due to the α chain, the compound is named as a compound with substituents added to position

two instead of the carboxyl group (position 1). Similarly, when the carbon number decreases due to the ω chain, the number of carbons decreases from position 20, and when there is an increase due to the ω chain, the compounds are named with the carbon atoms as substituents starting with the 21st atom. In addition, there are no particular rules with regard to configuration, and compounds are understood according to the configuration of the aforementioned basic skeleton. Consequently, a 15-keto PG compound having ten carbon atoms on the ω chain is named 15-keto-20-ethyl PG.

[0010]

The formula presented above shows a specific orientation in a typical configuration. In this specification, compounds are to be understood as having the aforementioned configuration when not otherwise specified. PGDs, PGEs or PGFs generally denote compounds having hydroxyl groups at position 9 and/or position 11 of the prostanoic acid, but the 15-ketoprostaglandin compound of the present invention is expanded to include compounds having other groups at position 9 and/or position 11. The aforementioned compounds are referred to as 9-dehydroxy-9-substituted or 11-dehydroxy-11-substituted compounds.

[0011]

As described above, naming of 15-keto PG compounds in this specification is carried out based on the prostanoic acid skeleton. If this naming is carried out according to IUPAC, for example, 13,14-dihydro-15-keto-16R,S-fluoroPGE_2 is named (Z)-7-{(1R,2R,3R)-3-hydroxy-2-[(4R,S)-fluoro-3-oxo-1-octyl]-5-oxo-cyclopentyl}-hepto-5-enoate;
13,14-dihydro-15-keto-20-ethyl-11-dehydroxy-11R-methylPGE_2 methyl ester is 7-{(1R,2S,3S)-3-methyl-2-[3-oxo-1-decyl]-5-oxocyclopentyl}hepto-5-enoate;
13,14-dihydro-6,15-diketo-19-methylPGE_2 ethyl ester is ethyl 7-{(1R,2S,3S)-3-hydroxy-2-(7-methyl-3-oxo-1-octyl)-5-oxo-cyclopentyl}-6-oxoheptanoate.
13,14-dihydro-15-keto-20-ethylPGF_2 α-isopropyl ester is isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydro-2-{3-oxo-1-decyl}cyclopentyl]-hepto-5-enoate; and
13,14-dihydro-15-keto-20-methylPGF_2 α-methyl ester is methyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-{3-oxo-1-nonyl}-cyclopentyl]-hepto-5-enoate.

[0012]

The 15-keto PG compound used in the present invention is any PG derivative having an oxo group instead of a hydroxyl group at position 15, and in addition, there can be a single bond (15-keto PG type 1 compounds) or a double bond (15-keto PG type 2 compounds) between positions 5 and 6 or two double bonds between positions 5 and 6 and positions 17 and 18

(15-keto PG type 3 compounds). Typical examples that can be used in the present invention include 15-keto PG type 1, 15-keto PG type 2, 15-keto PG type 3, 13,14-dihydro-15-keto PG type 1, 13,14-dihydro-15-keto PG type 2 and 13,14-dihydro-15-keto PG type 3 compounds and derivatives thereof.

[0013]

Examples of substituents or derivatives are compounds in which the carboxyl group at the terminus of the α chain of the aforementioned 15-keto PGs is esterified, physiologically acceptable salts, compounds having a triple carbon-carbon bond between positions 5 and 6 or a carbon-carbon double bond between positions 2 and 3, compounds having substituents on the carbon atoms of positions 3, 5, 6, 16, 17, 19 and/or 20, and compounds having lower alkyl groups or hydroxy (lower) alkyl groups instead of the hydroxyl group of position 11.

[0014]

In the present invention, an alkyl group with a carbon number of 1-4 can be presented as an example of a substituent that is bonded to the carbon atoms of position 3, 17 and/or 19, with specific examples being a methyl group and ethyl group. Examples of substituents that are bonded to the carbon atom of position 16 include a methyl group, ethyl group or other lower alkyl group, hydroxyl group or chlorine, fluorine or other halogen atom, or a trifluoromethylphenoxy group or other aryloxy group. Examples of substituents for the carbon atom of position 17 include a chlorine, fluorine or other halogen atom. Examples of substituents that are bonded to the carbon atom of position 20 include a saturated or unsaturated lower alkyl group such as a C_{1-4} alkyl, a lower alkoxy group such as C_{1-4} alkoxy, or a C_{1-4} alkoxy-C_{1-4} alkyl group or other lower alkoxyalkyl group. Examples of substituents for the carbon atom of position 5 include a chlorine, fluorine or other halogen atom. Examples of substituents for the carbon atom of position 6 include an oxo group that forms a carbonyl group. The configuration of the groups when a hydroxyl group, lower alkyl group or lower (hydroxy)alkyl group substituent is present at positions 9 and 11 can be the α or β form, or a mixture thereof.

[0015]

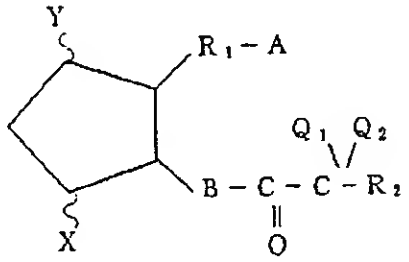
In addition, the aforementioned derivative can also be a compound wherein an alkoxy group, phenoxy group, phenyl group or other substituent is present on the ω terminal of a compound wherein the ω chain is shorter than in natural PGs. Particularly desirable compounds are compounds wherein a methyl group, ethyl group or other lower alkyl group is present on the carbon atom of position 16, compounds having a chlorine, fluorine or other halogen atom, compounds having a chlorine, fluorine or other halogen atom on the carbon of position 17 [sic],

compounds having a methyl group, ethyl group or other lower alkyl group on the carbon of position 19, compounds having a chlorine, fluorine or other halogen atom on the carbon atom of position 5, compounds having an oxo group on the carbon atom of position 6, compounds having a methyl group, ethyl group or other lower alkyl group on the carbon atom of position 20, and compounds in which a phenyl group or phenoxy group that can have substituents such as a halogen atom or haloalkyl group is bonded to the carbon atom of position 16 instead of the alkyl chain that is present subsequent to the carbon atom of position 16.

[0016]

Compounds that are preferable to use in the invention are those of formula I:

[Structure 2]



(I)

(in the formula, X and Y denote hydrogen atoms, hydroxyl groups, halogen atoms, lower alkyl groups, hydroxy (lower) alkyl groups or oxo groups (where at least one of X and Y is a group other than a hydrogen atom, and the five-membered ring can have one or more double bonds), A denotes $-CH_2OH$, $-COCH_2OH$, -COOH or functional derivatives thereof, B denotes $-CH_2-CH_2-$, -CH=CH- or -C≡C-, Q_1 and Q_2 denote hydrogen atoms, halogen atoms or lower alkyl groups, R_1 denotes a divalent lower to middle aliphatic hydrocarbon residue that is saturated or unsaturated, and is unsubstituted or is substituted with a halogen atom, oxo group or aryl group, and R_2 denotes a lower to middle aliphatic hydrocarbon residue that is saturated or unsaturated, and is unsubstituted or is substituted with an oxo group, hydroxyl group, lower alkoxy group, lower alkanoyloxy group, lower cycloalkyl group, aryl group or aryloxy group, or a lower cycloalkyl group, aryl group or aryloxy group).

[0017]

In the formula above, the term "unsaturated" in reference to R_1 and R_2 means that the compound has at least one double bond and/or triple bond for one of the carbon-carbon bonds of the primary chain or side chain, which bonds are solitary, separated or connected. According to common nomenclature, an unsaturated condition between two locations that are connected is represented by displaying the lower position number, and an unsaturated condition between two unconnected positions is indicated by displaying both position numbers. Preferred unsaturation is double bonding at position two and double bonding or triple bonding at position 5.

[0018]

The term "lower to middle aliphatic hydrocarbon" denotes a linear or branched hydrocarbon with a carbon number of 1-14 (where the side chains preferably have carbon numbers of 1-3), and compounds wherein R_1 is a hydrocarbon with a carbon number of 4-10 and R_2 is a hydrocarbon with a carbon number of 1-10 are preferred. The term "halogen" denotes a fluorine, chlorine, bromine or other such atom, and the term "lower" includes groups having carbon numbers of 1-6, when not otherwise specified. The term "lower alkyl group" denotes a saturated hydrocarbon group that is linear or branched and has a carbon number of 1-6, examples of which include a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and hexyl group. The term "lower alkoxy group" denotes a lower alkyl-O- group, and is defined as above.

[0019]

The term "hydroxy (lower) alkyl group" denotes the aforementioned type of alkyl group that is substituted with at least one hydroxyl group, examples of which include hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 1-methyl-1-hydroxyethyl groups. The term "lower alkanoyloxy group" denotes a group that can be represented by the formula RCO-O- (where RCO- denotes an acyl group such as an acetyl group produced by the oxidation of the aforementioned type of lower alkyl group). The term "lower cycloalkyl group" denotes a group that is generated by ring closure of the aforementioned type of lower alkyl group containing three or more carbon atoms, examples of which include a cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl group.

[0020]

The term "aryl group" includes an aromatic carbon ring or heterocycle (preferably, a monocyclic group) that can be substituted, examples of which include a phenyl, tolyl, xylyl and thienyl group. Examples of substituents include a halogen atom and a halogen-substituted lower alkyl group (where the halogen atoms and lower alkyl groups have the same meanings as above).

The term "aryloxy group" denotes a group expressed by the formula ArO- (where Ar is the aforementioned type of aryl group).

[0021]

The term "functional derivative" of the carboxyl group expressed by A includes salts (preferably pharmacologically acceptable salts), esters and amides. Examples of appropriate "pharmacologically acceptable salts" include common nontoxic salts, such as alkali metal salts (including sodium and potassium salts), alkaline-earth metal salts (including calcium and magnesium salts), ammonium salts, and salts with organic bases, for example, amine salts (such as methylamine salts, dimethylamine salts, cyclohexylamine salts, benzylamine salts, piperidine salts, ethylenediamine salts, ethanolamine salts, diethanolamine salts, triethanolamine salts, tris(hydroxymethylamino)ethane salts, monomethylmonoethanolamine salts, lysine salts, procaine salts, and caffeine salts), basic amino acid salts (for example, arginine salts and lysine salts), and tetralkylammonium salts. These salts can be manufactured from corresponding bases and acids by salt exchange or by common methods.

[0022]

Examples of esters include methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, 1-cyclopropylethyl ester and other lower alkyl esters, vinyl esters, allyl esters and other lower alkenyl esters, ethynyl ester, propynyl ester and other lower alkynyl esters, hydroxyethyl ester and other hydroxy (lower) alkyl esters, methoxymethyl ester, 1-methoxyethyl ester and other lower alkoxy (lower) alkyl esters and other such aliphatic esters and, for example, phenyl ester, tosyl ester, t-butylphenyl ester, salicyl ester, 3,4-dimethoxyphenyl ester, benzamidophenyl ester and other desirably substituted aryl esters, and benzyl ester, trityl ester, benzhydryl ester and other aryl (lower) alkyl esters. Examples of amides include methylamide, ethylamide, dimethylamide and other mono- or di- lower alkylamides, anilide, toluidide and other arylamides, methylsulfonylamide, ethylsulfonylamide, tolylsulfonylamide and other alkyl or arylsulfonylamides.

[0023]

Examples of preferred A groups include -COOH, $-COOCH_3$, $-COOCH_2CH_3$, $-COOCH(CH_3)_2$ and $-CONHSO_2CH_3$. In structure (I) above, the configuration of the α and/or ω chain can be the same as, or different from, the configuration of natural prostaglandins, but the present invention also includes mixtures of compounds having natural configurations and compounds not having natural configurations.

[0024]

Examples of typical compounds of the invention include 15-keto PGs, 13,14-dihydro-15-keto PGs, 6-oxo derivatives, Δ^2-derivatives, 3R,S-methyl derivatives, 6-keto derivatives, 5R,S-fluoro derivatives, 5,5-difluoro derivatives, 16R,S-methyl derivatives, 16,16-dimethyl derivatives, 16R,S-fluoro derivatives, 16,16-difluoro derivatives, 17S-methyl derivatives, 17R,S-fluoro derivatives, 17,17-difluoro derivatives, 19-methyl derivatives, 20-methyl derivatives, 20-ethyl derivatives, 19-desmethyl derivatives, 2-decarboxy-2-(2-carboxyethyl) derivatives and 16-debuchiru [transliteration]-16-phenoxy derivatives.

[0025]

When saturation occurs at positions 13 and 14 in the 15-keto PGE compound used in the present invention, there are cases where a keto-hemiacetal equilibrium is produced due to the formation of a hemiacetal between the keto moiety of position 15 and the hydroxyl moiety of position 11. When these types of tautomers are present, the occurrence of the two isomers changes depending on the type of substituents or the structure of the other moieties, and in some cases, one isomer comes to be predominantly present. In this invention, however, both are incorporated, and the compound is expressed based on its structural formula or nomenclature of the keto form regardless of the existence of these types of isomers. However, this is a matter of convenience, and is not intended to neglect the hemiacetal-form compound. In the invention, it is possible to use tautomers, mixtures thereof, optical isomers or mixtures thereof, racemic mixtures and other stereoisomers with the same objective.

[0026]

Some of the compounds that are used in the present invention can be manufactured by means of the methods described in Japanese Kokai Patent Application Nos. Sho 64[1989]-52753, Hei 1[1989]-104040, Hei 1[1989]-151519 and Hei 8[1996]-48665. These compounds can also be manufactured by means of other methods such as existing methods or methods that are similar to those described above.

[0027]

The compound that is used in the present invention can be used on animals and humans, specifically as an agent for hair generation and growth. Ordinarily, the compound is used externally at the local site where hair generation and growth is required. The dosage depends on the condition of the area to be treated, the desired effects, the dosing method and the treatment period, but ordinarily, when administered 2-4 times per day in a manner whereby it is retained, or when administered at 0.01-100 μg/affected area, sufficient effects are ordinarily obtained at a

dose of 0.001-500 mg/kg. The topical agent used in the invention can be a topical liquid or ointment. Topical liquids are produced by dissolving the effective component in a sterile aqueous solution such as physiological saline or buffer, or by combining the two for dissolution at the time of use. Ointments are produced by mixing the effective component in a base.

[0028]

Application examples

The present invention is described in additional detail below based on formulation examples and test examples, but the present invention is not restricted by these examples.

Formulation examples

Example 1 (ointment)

13,14-dihydro-15-keto-16,16-difluoro PGE_2 was mixed with the gel base indicated below at 20 μg/g.

Propylene glycol	10 g
Carboxymethyl cellulose	10 g
Sterilized purified water	80 g

[0029]

Test example

Test method

After preparatory raising of 8-week-old mice (C3H line male mice, bodyweight at time of testing = 26.3 ± 1.3 g) for 3 weeks, the hair on the back region was cut with scissors to produce a 2.5 x 2.5-cm-square region. The day of cutting was taken as day one, and starting on day 3, a solution containing the substance to be tested was applied at 0.3 mL per application per day for 20 days to the cut region. The solution containing the substance to be tested was used in testing after dissolving it in reagent-grade ethanol (Kishida Kagaku) to a concentration of 20 μg/m [sic; 20 μg/mL]. Reagent-grade ethanol (Kishida Kagaku) alone was used for the control group.

[0033]

Table II

① 試験群	② 毛長(Mean±SD：mm)
③ 第1群 対照(エタノール)	6.34±0.17mm
④ 第2群 被験物質20μg/ml	6.63±0.12mm*

⑤ *：p<0.01 Student's t検定

Key: 1 Test group
2 Hair length (mean ± SD: mm)
3 Group 1 Control (ethanol)
4 Group 2 (test substance 20 μg/mL)
5 *: $p < 0.01$ Student's t test